functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, and

(2) a pharmaceutically acceptable carrier.

79 (New). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a purified polypeptide of the *Helicobacter pylori* CAI antigen, which polypeptide: (i) comprises at least ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

80 (New). The vaccine of claim 70, wherein said second polypeptide comprises at least fifteen amino acids.

REMARKS

Claims 38 - 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59 - 70 were pending in the application.

Claims 38, 39, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59 -70 have been rejected.

By way of this amendment, claims 67 and 69 are canceled, claims 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59 - 63, and 70 are amended, and new claims 71 - 80 are added.

Upon entry of this amendment, claims 38 - 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59 - 66, 68, and 70 - 80 will be pending.

In view of the amendments presented herewith and the following remarks, Applicants respectfully request that the final rejection of the claims be reconsidered and withdrawn.

Summary of Amendment

Claims 67 and 69 are canceled without prejudice.

Claims 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59 - 63, and 70 are amended to clarify and more accurately describe that which is claimed. Support for these amendments is found in the original claims and throughout the specification as originally filed (for example, at page 14, lines 24 - 27 and at page 16, lines 19 - 29). No new matter has been added.

New claims 71 - 80 are added for consistency and to refer to specific embodiments of the invention. Support for new claims 71 - 80 is found in the original claims, and throughout the specification as originally filed (for example, at page 6, lines 12 - 15 page 7, line 38 through page 8, line 12, and page 38, lines 32 - 35). No new matter has been added.

Applicants note that in amending claims 50, 51, 53, 61, 63, and 70 to multiple dependent status, each now depends from a claim with a high number, because of the introduction of new claims. Applicants believe that this should cause no burden to the Examiner.

Additionally provided herewith is the unexecuted Declaration of Dr. Antonio Covacci pursuant to 37 C.F.R. §1.132 (the "Covacci Declaration"). The executed Covacci Declaration will be forwarded in due course.

Drawings

Pursuant to 37 C.F.R. §1.85(c), formal drawings will be filed within 3 months of the mail date of a Notice of Allowability.

Claim Objections

The Examiner has objected to claims 67 and 69 for lacking a period at their respective ends. Claims 67 and 69 have been canceled without prejudice rendering this objection moot. Applicants respectfully request withdrawal of the objection.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 48, 50, 51, 53, 54, 56, 57, 59, 60 - 65, and 70 were rejected under 35 U.S.C. §112, first paragraph, and the Examiner alleged, at page 3 of the Official Action, that

> the specification . . . does not reasonably provide enablement for the prophylactic or therapeutic vaccine, nor the methods for making and using this vaccine.

Applicants respectfully traverse this rejection.

The enablement requirement of 35 U.S.C. §112 is satisfied if a disclosure contains sufficient information such that persons of ordinary skill in the art, having the disclosure before them, would be able to make and use the invention. The legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Applicants respectfully submit that the reasoning and evidence offered in the Official Action is insufficient to support the conclusion that the claimed invention is not enabled. Applicants respectfully submit that one having ordinary skill in the art could practice the claimed invention without undue experimentation. Applicants respectfully submit that the requirements of the first paragraph of 35 U.S.C. §112 have been met.

Applicants note that, at page 4 of the Official Action, the Examiner "avers to the existence of animal models for the study of *H. pylori* infection and the existence of immunological screening assays for determining immunogenic fragments." However, at pages 4 - 5, the Examiner alleges that

> the existence of animal models does not support declarant's conclusion that these animal models would allow determination of prophylactic or therapeutic effect to be routinely carried out.

The Examiner supports this conclusion by reference to Exhibit E (Nedrud, 1999, *FEMS Immunol. Med. Microbiol.* 24:243-50), alleging that Exhibit E "contradicts Declarant's conclusion." Applicants respectfully disagree with the Examiner's reasoning.

The Examiner's comments, on page 5 of the Official Action, regarding §2.8.3 of Exhibit E do not negate enablement of the claimed invention. Any of numerous animal models of *H. pylori* infection that existed at the time of the earliest priority date for the present application can be used in a routine manner to evaluate the therapeutic or prophylactic efficacy of a vaccine preparation against *H. pylori* infection. The Examiner accepts the existence of such models of *H. pylori* infection, yet the Examiner fails to accept that the models could be used in a routine manner to test vaccine preparations. Applicants respectfully submit that nothing described by Exhibit E would alter the routine nature of using *H. pylori* infection models to test a candidate vaccine for its ability to prevent or treat *H. pylori* infection.

The animals used in the study described in §2.8.3 of Exhibit E were **immunodeficient** mice. Thus, that antibody-independent, protective mucosal immunity was demonstrated in that particular model has no bearing upon the general ability to evaluate a test vaccine in a model of *H. pylori* infection. Evidence of protection in the absence of antibodies in that particular model does not preclude that protection can be elicited with an antibody response. These mice have no B cells and, therefore, cannot produce antibodies.

While acknowledging that screening for linear epitopes was routine (page 5 of the Official Action), the Examiner alleged that "discovery of the protective epitope or epitopes would still be highly unpredictable and involve extensive, undue experimentation." The Examiner's arguments were based more upon predicting which conformational epitopes are therapeutic or prophylactic. Additionally, Applicants are not claiming **any** *H. pylori* antigen, but those from one particular *H. pylori* protein, which Applicants have sequenced. Additionally, the polypeptides which are effective as vaccines may comprise linear epitopes. Regardless, Applicants are not required to **predict** *a priori* which polypeptide portions or fragments of the entire CAI antigen protein will be

effective in prophylactic or therapeutic vaccines **before** testing. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219. Applicants only need to enable one of skill in the art to be able to identify, make, and use them without undue experimentation.

Applicants submit that the application as filed enables the invention as claimed. The specification discloses the nucleotide and amino acid sequence information for *H. pylori* CAI antigen (*see* specification at page 4, lines 33 - 34, page 51, lines 30 - 38, page 52, lines 15 - 17, and Figures 4A - 4F). Applicants have established that the generation of various polypeptides (full length and fragments) of the CAI antigen and the testing of these polypeptides as candidate prophylactic or therapeutic vaccines in the various animal models of *H. pylori* infection would have been routine (*see* Del Giudice Declaration, ¶¶10, 13, and 15 - 17). Applicants have effectively taught the skilled artisan how to make and use the claimed invention. The Examiner is reminded that whether or not experimentation is undue is not measured quantitatively, but qualitatively. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996); *see also In re Wands*, *supra*, 8 U.S.P.Q.2d at 1403-07.

As further support that animal models of *H. pylori* infection can be used for the testing the efficacy of vaccines comprising whole and fragments of *H. pylori* CAI antigen, Applicants submit Marchetti *et al.*, 1998, Vaccine, 16:33-7 ("Marchetti"), a copy of which is provided herein. Marchetti describes successful intragastric vaccine testing with an animal model. The focus of Marchetti was to assess the adjuvanticity of a non-toxic mutant of a mucosal adjuvant. VacA (cytotoxin) and CagA (CAI antigen), and certain fragments thereof, were tested for protective efficacy in the Marchetti study.

Although Marchetti ultimately reports that the particular CagA fragment tested (A17/12) did not yield what the authors call statistically significant protection, the criteria of a protective effect was very stringent. One hundred percent protection from **any** *H. pylori* growth was required. Marchetti states, at page 34, column 2, that "[m]ice were considered as 'not infected' when **no** *H. pylori* colony was detected on the plate on which the stomach was cultured." (Emphasis

supplied). A single colony, thus, was gauged as an infection. No information on the number of colonies observed was provide. Applicants' vaccine claims do not require that the protection elicited be 100%. The specification states, at page 15, lines 14 - 17

> [a] "vaccine" is an immunogenic, or otherwise capable of eliciting protection against H. pylori, whether **partial** or complete, composition useful for treatment of an individual.

(Emphasis added). Furthermore, while the authors concluded, based upon the stringent requirement, that the A17/12 CagA fragment did not confer significant protection to the mice, Marchetti also reports that this fragment **is** an immunodominant fragment in humans (see page 36, column 2).

The Examiner has alleged, at page 6 of the Official Action, that Exhibit F (Ghiara *et al.*, 1997, Infect. Immun., 65:4996-5002) and Exhibit G (PCT application PCT/IB99/00851) "fail to support enablement of the claimed invention." The Examiner alleges that the references submitted by Applicants support her enablement rejection, and her conclusion that "the effects of *in vivo* administration were poorly understood until recently." Applicants respectfully disagree and submit that the claimed invention is enabled by the application as filed.

"[T]he Examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation." M.P.E.P. §2164.04. The Examiner has not specifically identified the missing information, and therefore, has not effectively disputed the objective truth of the Applicants' assertion that the invention is enabled. Instead, the Examiner has pointed generally at the alleged unpredictability of the art. "Mere broad generalizations and allegations are insufficient for holding of non-enablement." *Ex parte Goeddel*, 5 U.S.P.Q.2d 1449, 1451 (B.P.A.I. 1987).

As the Examiner has acknowledged, "these two references demonstrate the vaccine potential of the CAI antigen." Exhibit G was relied upon by Applicants to show that mucosal delivery and mucosal adjuvants are, in fact, not required to achieve an effective *H. pylori* vaccine, and to refute the Examiner's assertion, at page 4 of the prior Official Action of February 14, 2000,

"that a mucosal adjuvant is required for vaccine efficacy." Exhibit F was relied upon by Applicants to show that vaccines comprising CAI antigen polypeptides can have a therapeutic, as well as protective effect.

Evidence that certain assumptions about the role of gastric antibodies were incorrect does not negate the ability of one skilled in the art to use *H. pylori* infection models to test candidate vaccines. In fact, such evidence supports enablement. As the Examiner acknowledges, Exhibit G indicates that a "systemic" protective effect can be achieved, and confirms that mucosal adjuvants are not necessary.

The Examiner has alleged (page 6 of the Official Action) that Exhibits F and G, as "post-filing documents cannot support enablement of a claimed invention unless the teachings of these documents follow the teachings of the specification." Applicants respectfully submit that it is well settled that while "a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling," it can be "offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative." *Gould v. Quigg*, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987). Applicants are not relying upon techniques and materials described in Exhibits F and G. Applicants submit that the claimed invention is enabled by the specification as filed. Rather, Applicants cite to Exhibits F and G to support operability of the claimed invention. Exhibits F and G bear out the fact that CAI protein can induce protection and treatment.

Applicants respectfully urge the Examiner to reconsider her position and recognize that one skilled in the art could practice the claimed invention based upon the original disclosure. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 48, 50, 51, 53, 54, 56, 57, 59, 60 - 65, and 70 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §102

Under 35 U.S.C. §102, the standard for anticipation is strict identity. A rejection based on anticipation requires a showing that each limitation of the claim be found within a single reference (*Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984)), either expressly or inherently. *Glaxo Inc. v. Novopharm Ltd.*, 34 U.S.P.Q.2d 1565,1567 (Fed. Cir. 1995).

The Examiner maintained the rejection of claims 38, 39, 42, 44, 45, 47, 48, 50, 54, and 56, and has now also rejected claims 66 and 68, under 35 U.S.C. §102(e) as allegedly being anticipated by Cover *et al.*, 1990, Infect. Immun., 58:603-610 ("Cover"). Applicants believe the Examiner intended to reject the claims under 35 U.S.C. §102(a), since Cover is a non-patent publication. Nevertheless, Applicants respectfully traverse this rejection.

The claims, as amended, recite (1) purified *H. pylori* CAI polypeptides (claims 38 and 39); (2) purified *H. pylori* CAI polypeptides comprising at least ten or at least fifteen amino acids, capable of inducing the production of anti-*H. pylori* antibodies, and exhibiting no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity (claims 42, 44, 45, 47, 66, and 68); and (3) vaccines comprising an immunologically effective amount of a purified *H. pylori* CAI polypeptide comprising at least ten or at least fifteen amino acids, capable of inducing the production of anti-*H. pylori* antibodies, and exhibiting no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity (claims 48, 50, 54, and 56).

At page 8 of the Official Action, the Examiner stated:

> Cover did in fact purify the CAI antigen in that the antigen was first present in a concentrated culture supernatant. The term "purified" is normally read to mean "that at least one step of purification has been carried out such that a purified antigen is more pure than the antigen in its natural context." (Exhibit F, page 7, lines 14-17). The instant specification however defines purified to mean that the antigen "is

> present in the substantial absence of other biological macromolecules of the same type." (Specification, page 16, lines 19-22). This definition has two problems: (1) the term "substantial" has not been defined; and (2) the Specification, page 7, line 27 uses the terms "same type" to refer to the same molecule being purified. The first problem is one of percentage of the purified antigen. The second problem shows that there exists an internal inconsistency in the definition. Since the definition provided by the Specification is ambiguous, the meaning that must be taken for the term "purified" is one consistent with the art recognized meaning as set forth in Exhibit G. Clearly the concentrated culture supernatant reads on the Exhibit's definition in that at least one step is performed to concentrate the antigen.

Applicants submit that, in the discussion of the phrase "same type" in the passage reproduced above, the Examiner intended to cite to **page 16** of Applicants' specification. The definition for the term "purified" appears at page 16 of the specification. Applicants further believe that, in the quoted definition for "purified" in the passage reproduced above, the Examiner intended to cite to **Exhibit G**, rather than Exhibit F.

The Examiner apparently chose to ignore the definition for "purified" that is provided in the specification. Instead, the Examiner adopted a definition that is extrinsic to the specification, alleging that the definition provided in the specification is ambiguous. This is inappropriate. The term "purified" is clearly and unambiguously defined in the specification.

At page 16, lines 19 - 29, the specification defines "purified" or "isolated" in reference to polypeptide or nucleotide sequences. With respect to a polypeptide, a polypeptide is "purified" or "isolated" when it "is present in the substantial absence of other biological macromolecules of the same type," *i.e.*, present in the substantial absence of other polypeptides. Applicants respectfully submit that the phrase "of the same type" does **not**, as alleged by the Examiner, "refer to the same molecule being purified." As it is used at page 16, line 22 of the specification, the phrase "of the

same type" clearly refers back to the beginning of the sentence, where a distinction is made between polypeptide or nucleotide sequence. One "type" of biological macromolecule is a polypeptide (or protein), the other "type" of biological macromolecule is a nucleotide sequence (or nucleic acid). When the phrase "of the same type" is used again at line 27 (as cited by the Examiner) the phrase logically carries the same meaning and is distinguishing between the two aforementioned biological macromolecule "types," *i.e.*, polypeptides versus nucleotide sequences. Applicants respectfully submit that one skilled in the art would find no ambiguity in this definition and would understand a purified polypeptide to be a polypeptide in the substantial absence of other, different polypeptides.

Moreover, contrary to the Examiner's assertion, the meaning of the term "substantial" is clear from the specification. The definition of "substantial" is implicit in the stated percentage weight of a particular polypeptide or nucleotide sequence in relation to the other biological macromolecules of the same type (other polypeptides or nucleotide sequences) that are present (specification at page 16, lines 22 - 29).

Regardless, the Examiner cannot disregard Applicants' definition and substitute one she finds supports her rejection, particularly one gleaned from a post-filing date reference. Claims are construed as of the time of filing. *Schering Corp. v. Amgen Inc.*, 55 USPQ2d 1650, 1654 (Fed. Cir. 2000).

Cover does not describe a purified 128 kDa protein. Cover describes a 128 kDa band obtained following electrophoresis of concentrated culture supernatants of *H. pylori* strains having vacuolizing activity. The band was recognized in immunoblots by human sera. The 128 kDa band that Cover describes has unclear immunogenic properties, and Cover reports that further characterization is needed, in light of the lack of recognition of the 128 kDa band by the rabbit serum (Declaration of Dr. Del Giudice ("Del Giudice Declaration"), submitted previously, ¶25), and its recognition by 6% of sera from non-infected people (Del Giudice Declaration ¶23).

Applicants submit that neither the preparation of a concentrated culture supernatant nor the immunoblotting analyses of Cover resulted in a "purified" 128 kDa protein as recited in the

claims. As explained in the Del Giudice Declaration (¶23), several contaminating proteins will be present, in proximity to, and in contact with, the protein of interest in an immunoblot. These proteins include proteins that were in the gel and transferred to the filter and all the blocking proteins contained in the milk-borate buffer used by Cover (*see* page 604, col. 2). Indeed, blocking proteins, such as casein and other milk proteins, occupy all the areas on the filter that were unoccupied following the transfer step. The 128 kDa band of Cover's immunoblots did not, therefore, represent a purified protein according to the definition provided by Applicants' specification, because it was not present in the substantial absence of other proteins.

Moreover, the preparation of a concentrated culture supernatant by Cover did not render the 128 kDa protein "purified" according to the definition of Applicants' specification, because it is not present in the substantial absence of other polypeptides. Those skilled in the art understand that the relative percentages of the different polypeptides in a concentrated culture supernatant are unchanged from the relative percentages prior to concentration. Thus, even under the definition selected by the Examiner, as articulated in Exhibit G at page 7, lines 15 - 16, the 128 kDa protein of Cover is no more pure in a concentrated culture supernatant than it is in its natural context.

Because Cover does not disclose or teach all of the limitations of the claimed invention, Applicants respectfully request that the rejection of claims 38, 39, 42, 44, 45, 47, 48, 50, 54, 56, 66, and 68 under 35 U.S.C. §102 be withdrawn. Applicants respectfully request an affidavit under 37 C.F.R. §1.104(d)(2), if this rejection is maintained.

Rejections under 35 U.S.C. §103

The Examiner maintained the rejection of claims 60 and 62 under 35 U.S.C. §103(a) as allegedly being obvious in view of Cover. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Examiner has failed to meet the criteria needed to support a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria.

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2142.

Claim 60, as amended, recites a method of preparing a prophylactic or therapeutic vaccine, comprising bringing a purified polypeptide of CAI that is at least ten amino acids in length, can induce the production of antibodies to *H. pylori*, and exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, into association with a pharmaceutically acceptable carrier. Claim 62, as amended, recites a method of preparing a prophylactic or therapeutic vaccine, comprising bringing a purified CAI polypeptide of SEQ ID NO:5 that is at least ten amino acids in length, can induce the production of antibodies to *H. pylori*, and exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, into association with a pharmaceutically acceptable carrier.

Applicants respectfully submit that it would **not** have been obvious to prepare the vaccines of claims 60 and 62, because Cover does not disclose or suggest a purified polypeptide of CAI antigen. Moreover, the Covacci Declaration, provided herein, attests to the difficulty of purifying the CAI antigen protein, due in part to its instability (at ¶8). Applicants were able to

prepare purified CAI antigen protein, because their method of culturing *H. pylori* and preparing material for gel electrophoresis were optimized to yield stable protein (Covacci Declaration at ¶¶10-12).

Newly presented claims 77 and 78 are also non-obvious. New claim 77 recites a method of preparing a prophylactic or therapeutic vaccine, comprising bringing a recombinant polypeptide of CAI that is at least ten amino acids in length, can induce the production of antibodies to *H. pylori*, and exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, into association with a pharmaceutically acceptable carrier. New claim 78 recites a method of preparing a prophylactic or therapeutic vaccine, comprising bringing a recombinant CAI polypeptide of SEQ ID NO:5 that is at least ten amino acids in length, can induce the production of antibodies to *H. pylori*, and exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, into association with a pharmaceutically acceptable carrier.

The Covacci declaration also attests to the difficulty in cloning of the CAI gene (¶14). Without a cloned gene, a recombinant protein is impossible to prepare. Thus, it would not have been obvious to prepare a vaccine comprising a recombinant polypeptide of CAI antigen. The cloning of the CAI gene was hampered by a lack of purified CAI protein and a lack of immunological reagents specific only for CAI. Applicants were able to prepare mouse polyclonal antibodies against CAI because Applicants were successful in purifying CAI protein (Covacci Declaration at ¶10). Furthermore, Applicants were able to generate a partial genomic library of *H. pylori* DNA, where others in the field had failed, because Applicants combined a particular cloning vector (pBluescript) with a particular strain of *E. coli* (DH10B) using a cloning strategy compatible with the AT-rich and unstable nature of the *H. pylori* genome (Covacci Declaration at ¶¶14 - 16). Applicants' success in preparing a genomic library ultimately enabled them to elucidate the nucleotide sequence for the entire CAI gene (Covacci Declaration at ¶16), making the preparation of recombinant CAI polypeptides and vaccines containing them possible.

The preparations used by Cover to immunize the rabbits were composed of 1) concentrated *H. pylori* culture supernatant, 2) formalinized, whole *H. pylori* cells, or 3) supernatant of French pressure cell-treated whole *H. pylori* cells. None of these preparations contained purified or recombinantly produced polypeptides of CAI antigen. Further, none contained a pharmaceutically acceptable carrier, as that term is used in Applicants' specification. The Examiner is directed to page 40, lines 16 - 21, of the application as filed. As is evident from the discussion therein, the pharmaceutically acceptable carrier is distinguished from diluents, such as water.

Applicants respectfully request that the rejection of claims 60 and 62 under 35 U.S.C. §103 over Cover be reconsidered and withdrawn.

Conclusion

Applicants respectfully submit that claims 38 - 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59 - 66, 68, and 70 - 80 are in condition for allowance. A notice of allowance is earnestly solicited. If the Examiner feels a telephonic interview would be helpful, she is asked to call the undersigned at 215-557-5901.

Correspondence

Applicants remind the Examiner that all correspondence from the Patent and Trademark Office concerning this application should continue to be sent to:

Alisa A. Harbin, Esq.
Vice President & Associate Chief Patent Counsel
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94608-8097

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned **"Version with markings to show changes made."**

Respectfully submitted,

Date: July 30, 2001

Robin S. Quartin
Registration No. **45,028**

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(215) 568-3100

Enclosures:
copy of Marchetti *et al.* (1998) *Vaccine* 16:33-7
copy of unexecuted declaration of Dr. Antonio Covacci with Exhibits A - C

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 67 and 69 are canceled without prejudice, and new claims 71 - 80 are added. The following are marked up versions of claims 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59 - 63, and 70, which are amended herein, showing all of the changes relative to the previous version of each.

42 (Twice amended). A purified polypeptide of the *Helicobacter pylori* CAI antigen, which polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

44 (Twice amended). The polypeptide of claim 42 which comprises at least [about] fifteen amino acids.

45 (Twice amended). A purified polypeptide of the *Helicobacter pylori* CAI antigen [amino acid set forth in SEQ ID NO:5], which polypeptide: (i) comprises at least [about] ten contiguous amino acids of SEQ ID NO:5, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

47 (Twice amended). The polypeptide of claim 45 which comprises at least [about] fifteen amino acids.

48 (Twice amended). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a recombinant polypeptide of the *Helicobacter pylori* CAI antigen, which polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

50 (Twice amended). The vaccine of claim 48 or 79 wherein said polypeptide comprises at least [about] fifteen amino acids.

51 (Twice amended). The vaccine of claim 48 or 79 further comprising an immunologically effective amount of a second polypeptide of the *Helicobacter pylori* heat shock protein, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

53 (Twice amended). The vaccine of claim 51 wherein said second polypeptide comprises at least [about] fifteen amino acids.

54 (Twice amended). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a recombinant polypeptide of the *Helicobacter pylori* CAI antigen [amino acid set forth in SEQ ID NO:5], which polypeptide: (i) comprises at least [about] ten contiguous amino acids of SEQ ID NO:5, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and

NEW

(iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

56 (Twice amended). The vaccine of claim 54 wherein said polypeptide comprises at least [about] fifteen amino acids.

57 (Twice amended). The vaccine of claim 54 further comprising an immunologically effective amount of a second polypeptide of the *Helicobacter pylori* heat shock protein, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

59 (Twice amended). The vaccine of claim 57 wherein said second polypeptide comprises at least [about] fifteen amino acids.

60 (Twice amended). A method of preparing a prophylactic or therapeutic vaccine comprising bringing into association:

(1) an immunologically effective amount of a purified polypeptide of the *Helicobacter pylori* CAI antigen, which polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, and

(2) a pharmaceutically acceptable carrier.

61 (Twice amended). The method of claim 60 or 77 further comprising adding an immunologically effective amount of a second polypeptide of the *Helicobacter pylori* heat shock protein, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

62 (Twice amended). A method of preparing a prophylactic or therapeutic vaccine [which] comprising bringing into association:

(1) an immunologically effective amount of a purified polypeptide of the *Helicobacter pylori* CAI antigen amino acid [set forth in SEQ ID NO:5], which polypeptide: (i) comprises at least [about] ten contiguous amino acids of SEQ ID NO:5, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, and

(2) a pharmaceutically acceptable carrier.

63 (Twice amended). The method of claim 62 or 78 further comprising adding an immunologically effective amount of a second polypeptide of the *Helicobacter pylori* heat shock protein, which second polypeptide: (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

70 (Amended). The vaccine of claim 48 or 79, further comprising an immunologically effective amount of a second polypeptide, wherein said second polypeptide is of the *Helicobacter pylori* cytotoxin (CT) protein, and (i) comprises at least [about] ten amino acids, (ii) can be used to induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits substantially no toxicity, or substantially reduced toxicity.